JAMES B. YOUNG, MD
CARLOS A. LEON, MD
HARTWELL H. WHISENNAND, III, MD
GEORGE P. NOON, MD
MICHAEL E. DeBAKEY, MD

Heart transplantation: no longer an experiment

The authors, The Multi-Organ Transplant Center of The Methodist Hospital and Baylor College of Medicine. Send reprint requests to Dr Young, 6535 Fannin, SM-491, Houston, TX 77030.

The therapeutic benefit of cardiac transplantation is emphasized by the high quality of life that recipient patients demonstrate. Furthermore, 20 years after the initial faltering attempts at human heart transplantation, survival rates have dramatically improved. In patients otherwise faced with a 90% probability of death within one year, transplantation often results in survival of more than 80%. Reasons for this progress include better cardiovascular surgical technique, more sophisticated immunosuppressive drugs, and increased understanding of rejection dynamics. Additionally, we have more therapeutic agents to treat complications after transplantation, and we have a better idea of which patients are likely to benefit. We review the development of the concept and science of heart transplantation, putting our present knowledge into perspective.

KEY WORDS: CARDIAC TRANSPLANTATION, HEART FAILURE, CARDIOMYOPATHY, IMMUNOSUPPRESSION.

Cardiac transplantation is now a therapeutic option for patients with end-stage heart disease. Indeed, hospitals in Austin, Dallas, Houston and San Antonio perform this procedure, and there may be over 100 heart transplant "centers" in the United States (1). Solid organ transplantation in general is quite frequent. In 1986, more than 11,000 solid organs were transplanted, including 1,430 hearts (1). Improved graft and patient survival associated with these transplants relates to new antirejection medications (including cyclosporine and OKT3), the ability to diagnose organ rejection early, lower maintenance steroid doses, and improved diagnostic techniques and treatment protocols for infection. Additionally, patient selection has become sophisticated with well-defined criteria predicting success. Development of cardiac transplantation as a therapeutic option, in many respects, resembled the progress of renal transplantation, but occurred decades later. The earliest heterotopic transplant of a cadaveric kidney, for example, occurred in 1947. This was done in an anuric pregnant woman who was in severe shock and uremic coma (2). The transplanted kidney produced urine and was removed 48 hours later. The patient recovered. Renal transplantation, however, brought much social and legal debate that spilled over into the early years of heart transplantation as well. Common problems included patient selection, finding suitable organ donors, creating new definitions of death, and handling problems of immunosuppression.

Cardiac transplantation evolved from a highly theoretical and experimental concept to a procedure of proven therapeutic benefit. Much of the basic groundwork for heart transplantation was laid in the early part of this century when Carrel published his protocols for heterotopic canine heart transplants (3,4). These studies actually were designed to pioneer vascular anastomotic technique, so important to cardiovascular surgery in general, but also demonstrated the feasibility of placing an explanted heart in heterotopic position (the animal's neck). The problem of cell-mediated rejection of transplanted hearts was recognized in 1933 by Mann and associates (5), and Luisada's group in 1951 first speculated seriously about the therapeutic potential of heart transplantation in humans (6): "A transplanted heart or heart-lung transplantation might be used for replacement of the diseased organ. The latter must be considered, at present, a fantastic dream and does not fall within the scope of present considerations."

Downie in 1953 (7) demonstrated that heart transplantation in experimental animal preparations was possible with simple techniques. Between 1957 and 1959, Webb et al (8) demonstrated the effectiveness of hypothermic myocardial preservation by completing the first orthotopic canine heart transplantations from which the recipient animals awoke (9). In 1958, Goldberg did the first orthotopic canine transplant utilizing cardiopulmonary bypass (10,11), and in 1959 Cass and Brock refined the implantation technique using methods that were ultimately extrapolated to human heart transplants (12). Lower and Shumway in the 1960s reported their technique for canine heterotopic transplants that allowed animals to return, for the first time, to normal function (13,14). It was their observation in 1961 that control of transplant organ rejection was now the most important challenge (15). They noted: "Observations in [our] animals suggest that, if the immunologic mechanisms of the host were prevented from destroying the graft, in all likelihood it would continue to function adequately for the normal lifespan of the animal." This was a seminal observation, appropriately directing research toward control of the rejection problem.

Subsequent efforts in the 1960s were focused toward technique development, with Reemtsma (16) and Demikhov (17) refining heterotopic (parallel or "piggyback") transplants. In 1965, Kondo demonstrated long-term orthotopic transplant survival in immunologically immature puppies (18), and Lower showed that exogenous immune suppression allowed long-term survival in his canine transplant model (19). It was during these experiments that a decrease in electrocardiographic QRS voltage was correlated with significant rejection.

It is apparent that a cadre of investigative information, produced over a 60-year period, was responsible for setting the stage for the first clinical trials of human heart transplantation. Early ventures

into human heart transplantation were controversial. Hardy et al actually reported the first human heart transplant (20). In January 1964, they implanted a xenographic transplant (a chimpanzee heart) in a patient in Jackson, Miss. The small primate heart was unable to support the patient's circulation, however, and cardiopulmonary bypass could never be terminated. In 1966, it was shown that one could remove a human heart from a cadaveric renal donor, and then successfully reimplant the organ and establish an appropriate rhythm. A human heart was also successfully transplanted into a baboon (21).

The first orthotopic allograft heart transplant was performed by Barnard on Dec 3, 1967, in Capetown, South Africa (22). The patient survived 18 days, dying of pneumonia and sepsis. The first human orthotopic heart transplant in America was done two weeks later in Brooklyn, New York, when Kantrowitz placed an anencephalic infant's heart into an 18-day-old patient with a terminal congenital cardiac anomaly (23). The recipient infant only lived several hours. It is interesting that the sociologic debate about use of anencephalic infants as organ donors is just now beginning to peak, 20 years after this situation was first described. Subsequently, between 1968 and 1970, approximately 100 heart transplant procedures were performed in 17 countries, with almost one third of these operations done in Texas (The Methodist Hospital and St Luke's Episcopal Hospital in Houston) (24).

The initial attempts at cardiac transplantation in the late 1960s met multiple and, most of the time, overwhelming problems, usually surrounding organ rejection and host infection. New and better approaches to the management of these challenges were necessary before this procedure could be accepted as therapeutic and not experimental. As mentioned, the 12 patients receiving transplants in 1968 and 1969 at The Methodist Hospital and Baylor College of Medicine were an important part of this early experience (25). Interestingly, two survived a significant period of time (four and six years). The majority of deaths in this group, however, happened early and were caused either by acute rejection of the transplanted organ or by overwhelming infection. Because of these problems, most centers abandoned the procedure in the early 1970s and established a moratorium on cardiac transplantation (26). With new drugs (particularly cyclosporine) available to modulate rejection, reemergence of heart transplant programs began in the early 1980s. Heart transplantation was reestablished in 1982 at the Texas Heart Institute, St Luke's Episcopal Hospital (27), and in 1984 at The Methodist Hospital and Baylor College of Medicine (28). Programs are now established in Austin, Dallas, and San Antonio as well.

Recent advances in transplantation, particularly the commercial availability of cyclosporine, have led to new and impressive results. We can now expect longer graft survival and virtually normal lifestyles in carefully selected patients. The experience reported by the International Registry of Heart Transplantation suggests that the one-year survival rate in patients receiving orthotopic cardiac transplantation is approximately 80% and the five-year survival rate is over 60% (29). Patients who live past the first year are very likely to live at least five years. It is of interest to note that a recent report described a 43-year-old Italian heart transplant patient who successfully completed the New York marathon (30). Currently the longest surviving heart transplant recipient has lived with his transplant for 15 years and continues to do quite well (31). Previously, the longest living heart transplant recipient had a relatively normally functioning heart for 18 years and died of a pulmonary complication. This individual was quoted on the 15th anniversary of his operation as saying he would probably "die at 100, shot by a jealous husband" (32).

The therapeutic benefit of cardiac transplantation is again emphasized when death rates are analyzed for patients with end-stage heart disease who are selected for cardiac transplantation but receive no appropriate donor-matched organ (33). In some programs, there has been a 100% mortality in this group within several months. Indeed even in patients who were not thought to be "sick enough" for heart transplantation, the mortality has been extraordinarily high (34). Statistics, generally, for patients with severe congestive cardiomyopathy spell doom, with a life expectancy ranging from six months to two years (35). Additionally, these patients have a miserable existence with continuous and sometimes profound weakness, fatigue, dyspnea, and orthopnea. They are, frequently, completely bedridden and, often, terminally hospitalized. Transplantation, therefore, in individuals having no pharmacotherapeutic regimen to which they would respond, obviously provides hope and, if successful, dramatic relief.

Selection of candidates for cardiac transplantation

Consideration of cardiac transplantation should be limited to those individuals who have intractable congestive heart failure and are seriously disabled but have no significant damage to other vital organs. Patients are generally classed as New York Heart Association clinical classification III or IV. This means that patients are symptomatic with weakness, fatigue, and dyspnea at rest or with minimal exertion. They are generally unable to work and confined to relatively sedentary activity levels. This results from end-stage cardiac disease caused by idiopathic dilated cardiomyopathy, coronary artery disease with ischemic left ventricular dysfunction, or end-stage valvular and hypertensive heart disease. Patients with infiltrative cardiomyopathies causing end-stage symptoms (sarcoidosis, hemochromatosis, and amyloidosis) may not be suitable for transplantation since these difficulties may recur in the transplanted heart. Recurrent amyloid is seen in renal transplant patients, for example (36). Heart transplantation has, however, been performed in a few individuals with these disease processes, and short-term attenuation of difficulties have been documented (37). Since these diseases do recur in the transplanted heart, patients of this sort should be given a low priority when compared to those with other forms of end-stage heart disease. Patients with acute myocarditis and heart failure have traditionally been given a therapeutic course of immunosuppressive agents before consideration of heart transplantation because of the possibility of improving their left ventricular function. Unfortunately, treatment protocols are not well established. Indeed, there even is controversy about whether treating these patients is effective. Individualized judgment seems appropriate. An additional interesting arena is transplantation for patients with untreatable malignant ventricular arrhythmias. Individuals with episodes of recurrent sudden cardiac death uncontrolled by standard therapeutic intervention, including pharmacotherapeutic manipulation and surgical therapy, might be cured with treatment by cardiac transplantation. Anthracycline-induced cardiomyopathy may also be an indication for transplantation, but the underlying disease precipitating the need for these drugs must have been resolved.

All patients considered for heart transplantation should meet several physiologic and psychosocial criteria. Additionally, certain financial obligations may have to be met by the patient. A pretransplantation evaluation should be designed to identify underlying systemic illnesses that might hamper eventual recuperation following cardiac transplantation. There must be no irreversible damage to the central nervous system, liver, or kidneys. It is important that a thorough review of the patient's medical history and a complete physical examination be performed. Particular attention is paid to the possibility of occult active infection, the presence of fixed pulmonary hypertension, recent pulmonary embolus, concurrent malignancy, or diabetes mellitus requiring insulin therapy. Though some programs have allowed insulin-dependent diabetics to receive heart transplants, we do not (38).

Routine laboratory tests are undertaken as part of the preoperative evaluation. These include complete blood count, urinalysis, electrocardiogram; chest roentgenogram; panorex view of the teeth; pulmonary function studies; determinations of levels of blood urea nitrogen, creatinine, electrolytes, bilirubin, alkaline phosphatase, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), lactate dehydrogenase (LDH), two-hour postprandial blood sugar; 24-hour urine testing for creatinine clearance; ABO and RH blood typing, and HLA tissue typing. Patients are also screened for previous exposure to Epstein-Barr virus, herpes, cytomegalovirus, as well as tuberculosis, fungal disease, hepatitis, and toxoplasmosis. These studies are of particular importance postoperatively when there may be reactivation of latent viral infection or transmission of one of these agents from a donor to the recipient.

Candidates for cardiac transplantation should also undergo a complete right and left heart catheterization study, and in some cases, endomyocardial biopsy. This is done to determine the etiology of congestive heart failure, selecting individuals that may benefit from alternative therapeutic adventures. For example, some patients may clinically improve with coronary artery bypass grafting, resection of left ventricular aneurysm, correction of valvular or architectural abnormalities, immunosuppressive therapy of inflammatory myocarditis, or the use of new or experimental vasodilators and inotropic agents.

In addition to these studies, it is important to assess the patient's psychosocial support system. The patient should demonstrate an ability to cooperate and understand medical treatment programs. He or she must be willing to accept the risks of cardiac transplantation and be committed to long-term follow-up, as well as a long and stressful preoperative wait. A strong supportive family unit of one sort or another is critical in assisting the medical personnel during the stresses and rigors of the preoperative and postoperative periods. Of additional importance, the patient must have sufficient financial resources to pay for expenses (such as travel and lodging before and after transplantation) not covered by insurance or other health care beneficiaries.

Fig 1 summarizes the major criteria for recipient selection. The select patients, once chosen for cardiac transplantation, have a median survival of less than one year without transplantation. It is estimated, however, that there are approximately 1,000

1. Criteria for acceptable cardiac transplant recipient.

Terminal heart disease otherwise untreatable
Absence of compromising systemic disease process
Reasonable physiologic age
Normal hepatic and renal function
Absence of active infection
No pulmonary infarction in preceding two months
No insulin-dependent diabetes mellitus
Psychologic stability and supportive social milieu

to 8,000 individuals per year in the United States who would be suitable candidates for cardiac transplantation but there may only be 1,000 to 3,000 donor hearts available each year (39). These figures highlight the critical importance of choosing the best available candidate and indicate the reason why a large percentage of patients die prior to transplantation. Additionally, early identification and evaluation of candidates for cardiac transplantation are important, so that one is not faced with the problem of trying to evaluate and prepare for transplant a desperately ill patient requiring maximum cardiovascular support in a short period of time.

The screening criteria listed above are designed to identify patients with the greatest opportunity for survival and rehabilitation following cardiac transplantation. Programs should, however, be willing to evaluate patients on an individual basis and have criteria with some flexibility.

Active infection must be excluded because of the necessity for postoperative immunosuppressive therapy for the rest of the patient's life. Similarly, patients with recent pulmonary infarction are particularly predisposed to the development of cavitary lung abscesses. High-dose steroids used for immunosuppression may make control of diabetes difficult, and in our opinion, insulin dependence becomes an exclusionary factor. The normal right ventricle of the transplanted heart cannot acutely adapt to a fixed increase in pulmonary vascular resistance, and acute right heart failure of the transplanted heart accounts for postoperative mortality in 5% of patients dying. Since active peptic ulcer disease may be exacerbated by postoperative stress and corticosteroids, these individuals should be excluded. Active drug addiction and excessive alcohol consumption are psychological factors that, in our opinion, mandate exclusion since these problems can have an adverse effect on patients' long-term outcome. Because prior thoracotomy may create substantial mediastinal fibrosis causing difficulty with heart amputation, patients with multiple prior surgical procedures within the chest must be carefully considered. Preexisting malignancy and bronchitis with obstructive pulmonary disease (and their predisposition to infection) are two common examples of coexisting diseases that might limit life expectancy and compromise recovery from cardiac transplantation. Contraindications to cardiac transplantation are listed in Fig 2. Age is only a relatively important factor. Individuals must have, physiologically speaking, end-organs that are stable and not likely to fail in the face of major operative interventions or immunosuppressive therapy, and age alone may not predict this. There is some suggestion that older patients may have a blunted immunologic response to organ transplantation and these individuals, ipso facto, should not be excluded from consideration (40). Indeed, we have had increasing experience in transplanting organs in patients over the age of 60. Of 12 patients transplanted in that decade of life (the oldest transplanted at age 68), there has been only one death.

2. Absolute contraindications to cardiac transplantation.

Fixed pulmonary hypertension (resistance >600 dynes cm^2 sec)
Significant peripheral or cerebrovascular disease
Active peptic ulcer disease
Unresolved pre-existing malignancy
Significant chronic bronchitis or chronic obstructive pulmonary disease
Co-existing illness limiting life expectancy
Disease likely to recur in the graft (amyloid, hemochromatosis)
ABO incompatibility between recipient and donor

Because patients with severe end-stage heart failure frequently require aggressive hemodynamic support, including total artificial heart or ventricular bypass systems, these patients are not necessarily eliminated as candidates for transplantation. Indeed, not infrequently patients require parenteral administration of inotropic drugs to maintain an adequate blood pressure and enhance renal perfusion prior to cardiac transplantation and intra-aortic balloon counterpulsation. Reports emphasize that these patients can successfully receive transplants as long as infection is not present and end-organ damage has not occurred (41). One of the most difficult decisions to make, however, is when to begin mechanical support. Survival clearly is not as great "bridging-to-transplantation" with the artificial heart, but even this aggressive intervention can produce positive results (42).

Selection of patients for a second or third cardiac transplant may be required. Severe and irreversible rejection can necessitate consideration of retransplantation shortly after the first operation. In other patients, chronic rejection or the development of accelerated obliterative coronary artery disease seems to result in graft failure. Guidelines for selecting patients for repetitive cardiac transplantation should be the same as for the initial procedure. Survival statistics, however, for repeat heart transplantation suggest that only one third of the patients survive an additional two years (43). The number of sequential cardiac transplantation procedures should be limited to extraordinarily carefully selected individuals.

Operative approaches

Successful heart transplantation is dependent upon donor organ referral and adequate medical management of these cases. Successful amputation of the donor heart is performed with appropriate cardioplegic technique, and the recipient patient must be stabilized preoperatively, sometimes with aggressive measures that include intravenous vasodilator and inotropic support or a variety of perfusion assist devices. Immediately before surgery, we routinely perform right heart catheterization of the recipient so that we can monitor and aggressively treat pulmonary hypertension, since this is one of the major problems limiting early success of heart transplantation. If pulmonary dynamics can be ameliorated, with systolic pressures brought below 60 mm Hg and pulmonary resistance less than 8 Wood units (approximately 600 dynes·cm^2·sec^{-5}), acute right heart failure occurs less often.

Amputation of the donor heart is done at the time of carefully orchestrated multi-organ harvesting, and a variety of surgical techniques are available. At times, organ harvesting is performed with patients placed on hypothermic cardiopulmonary bypass support allowing removal of kidneys, liver, heart, and lungs without compromise. An appropriately cardiopleged, cooled, amputated donor heart is placed in a 4°C (39.2°F) ice bath and transported to the site of the recipient who has been prepared in standard fashion for open heart surgery with pump support. Obviously, the longer the cold ischemic time, the greater the likelihood of myocardial cell damage. It is optimal, therefore, to transplant patients as rapidly as possible after amputation of the donor heart, and it makes sense to regionalize organ distribution for cardiac donors. Four hours is generally the upper limit of cold ischemic time that the amputated heart can tolerate; however, some hearts cooled for up to six hours functioned satisfactorily after implantation.

Implantation of the heart is done using either an orthotopic or heterotopic ("piggyback") technique (44–46). Orthotopic heart transplantation, where the native heart is completely removed and the donor heart placed in the normal mediastinal position, is generally the preferred approach. Survival, indeed, is much better with orthotopic transplants than with the piggyback technique. It may be, however, that the latter procedure is more often performed in extraordinarily ill patients or when the donor heart is considered marginal, skewing the data. When one has an appropriate size match (body weight, height, and surface areas within 10% to 20% of the donor) and the donor heart is without question in good shape (young donor without any abnormal cardiac findings), orthotopic implantation is our choice. If, however, there is a donor/recipient size mismatch with the donor heart being substantially smaller, or more recipient pulmonary hypertension is present than one ordinarily would be comfortable with, heterotopic implantation might be considered. Also, if there is any likelihood at all that the native heart might improve (such as if myocarditis were the reason for heart failure), or if profound rejection occurred in the graft, heterotopic transplantation would allow eventual removal of the piggyback implant. Disadvantages of this type of transplantation, however, include difficulty in obtaining endomyocardial biopsy specimens during long-term follow-up, the problem of eventual cessation of heartbeat in the native heart with subsequent thrombosis of its chambers, arrhythmias occurring in the native heart with marked decrement in augmentation of its part of circulatory flow, and the more complicated surgical procedure required. Furthermore, if heterotopic transplantation is done in patients with ischemic heart disease, these individuals may still have symptomatic angina pectoris. Heterotopic heart transplantation can also be plagued by difficulties associated with squeezing two hearts into the same mediastinum. Tamponade of either heart might result, kinking of a great vessel might develop, and atelectasis of adjacent lung can occur. For all of these reasons, we believe orthotopic heart transplantation is the preferential route, though certainly in some individuals use of the heterotopic approach seems warranted (Fig 3).

3. Advantages and disadvantages of heterotopic ("piggyback") heart transplant.

Advantages	Disadvantages
Can use smaller grafts	Technically difficult procedure
May overcome high pulmonary pressures	May cause tamponade
	Great vessels may kink
May remove graft	Difficult to perform biopsy
	May cause atelectasis
	Native heart may stop
	Angina still a problem

Postoperative patient management

Postoperative management of patients is focused on three areas: (a) ensuring hemodynamic integrity of the transplanted heart in the early period; (b) preventing rejection of the heart during the lifetime of the recipient; and (c) managing complications that develop from immunosuppressive therapy, including hypertension, renal and hepatic insufficiency, and infection.

Though operating at a remarkable level of function, the transplanted heart is not normal. Indeed, early in the postoperative period there seems to be rather significant right ventricular dysfunction with subsequent tricuspid insufficiency and, at times, atrial inactivity (47,48). Still, however, with time and gentle coaxing, systolic function of the heart is well preserved with ejection fraction usually above the 50% range. Rejection, however, can cause significant reduction in diastolic dysfunction because of cellular destruction with subsequent fibrosis. Diastolic dysfunction develops in virtually all transplant patients and may progressively worsen with time. This may be exacerbated by hypertension, but even without this, most hearts hypertrophy (49). Still, however, patients have remarkable levels of

compensation and are capable of doing extraordinary workloads.

Rejection is one great fear. Generally, patients survive the early postoperative period. It is rare for an implanted heart that has been harvested with care and not damaged previously to not function at the time of implantation. Occasionally, acute fulminant non-cell-mediated rejection occurs, with hearts stopping virtually immediately after perfusion with the recipient's blood. Problems with cell-mediated rejection usually begin several days after heart transplantation, and the only reliable method of assessing this is with endomyocardial biopsy. Biopsies are generally performed on a weekly basis for the first four to six weeks, and then at subsequent increasing intervals for the lifetime of a patient. A stable patient followed for six to 12 months after surgery may have biopsies scheduled only at yearly intervals. Unfortunately, one cannot predict rejection by electrocardiographic analysis, echocardiographic study, or radionuclide tests with enough accuracy to not have to perform routine biopsy. These ancillary tests, however, are extraordinarily helpful in putting biopsy findings into perspective. A tremendous amount of research is currently focused on methods to monitor, in a noninvasive fashion, rejection of transplanted hearts.

The majority of immunomodulation protocols today include cyclosporine. Generally, patients receive either loading doses intravenously, orally, or by continuous intravenous infusion early in the postoperative period. Patients also receive high-dose steroids and, frequently, azathioprine. Recently, OKT3, a new humoral immunomodulating drug, has been used to attenuate rejection early in the post-transplant period.

Complications must be sought aggressively. Cyclosporine's major difficulties are the hypertension it causes and the renal and hepatic insufficiency that can develop. Also lipids seem to rise in the post-transplant period, possibly due to altered hemodynamics and hepatic blood flow as well as to intrinsic effects of cyclosporine itself. Patients are aggressively counseled about low-salt, low-fat diets and given vasodilating, diuretic, and alpha-blocking compounds to control their blood pressure. Beta-blockers are avoided since these patients operate with a denervated heart and respond to exercise by recruiting catecholamine drive. Though beta-blockers can be used, it is generally felt they might precipitate difficulties during long-term therapy. Hepatic and renal dysfunction can usually be managed by lowering the cyclosporine dose, of course, at the risk of allowing rejection to occur.

Physicians must be vigilant about the development of infection in these patients, and any complaint that raises one's suspicion about either an acute or a chronic infection should be vigorously pursued so that early antimicrobial therapeutics can be begun.

Other long-term problems include the development of graft atherosclerosis. Once the one-year survival point has been reached, the most common cause of death in the heart transplant patient today seems to be myocardial infarction with sudden death precipitated by arrhythmias related to myocardial necrosis. Patients with heart transplants and obliterative coronary artery disease may have asymptomatic myocardial ischemia develop because of the denervated implant. They do not present with symptoms of angina pectoris. Cardiac arrhythmias, syncope, sudden death, and heart failure can be the first signs of this difficulty, but all of these problems can also develop in the rejecting heart.

Postoperative lymphoproliferative disorders and malignancies have also been reported in patients chronically immunosuppressed, particularly when cyclosporine and antilymphocyte globulin have been added to the regimen. It seems, though, that the majority of lymphoproliferative disorders seen (lymphoma), have been in patients whose initial problem was idiopathic dilated cardiomyopathy, suggesting that some subtle immune defect may account for both the initial disease and the late complication. Most of these tumors are radiosensitive lymphomas and unicentric. Lesions tend to occur within one year after transplantation, and frequently involve the gastrointestinal tract or peripheral lymph nodes. Both polyclonal and monoclonal tumors exist, and there is also an association between tumor production and Epstein-Barr virus exposure. If complications such as bowel rupture can be surmounted or avoided, tumors generally respond to a combination of radiotherapy, resection, and reduction in immunosuppressive regimen. It should be emphasized that these disorders are very responsive to radiotherapy and that treating these individuals with antineoplastic drugs might actually be dangerous.

Long-term follow-up

Most heart transplant recipients can look forward to leading relatively normal lives. Reports suggest that the vast majority of surviving cardiac transplant patients are New York Heart Association Functional Class I, and their only restrictions are generally those dictated by common sense. Patients should pursue good health habits including regular, vigorous activity, maintenance of ideal body weight, attention to cholesterol and saturated fat intake, and avoidance of cigarette smoking. The latter is of particular importance given that the lungs are the most frequent site of infectious complications and that the patients are at risk, already, for the development of graft atherosclerosis.

Second frontiers of cardiac transplantation

Unlike 20 years ago, when the major impediment to successful heart transplant was control of the rejection process, challenges today relate more to making enough donor organs available for all patients currently on the waiting list (800 patients in December 1987), attenuating the complications of cyclosporine (particularly hypertension and renal and hepatic insufficiency), and elucidating the cause and natural history of the obliterative coronary artery disease that develops. We are certain that these problems, like others, will be minimized.

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